REMARKS/ARGUMENTS

The claims have not been amended but are reproduced above for ease of reference.

The paragraph numbering of the office action is used in responding to the Examiner's comments. Lack of comment on any of the Examiner's remarks should not be construed as agreement therewith.

¶¶7-9. Applicant reiterates willingness to provide a terminal disclaimer should the claims be found otherwise allowable.

¶10. Claims 1, 2, 4, 10-12, 22-24, 31, 32, 36, 82-84, 88-90, 95-99, 101, 103, and 104 stand rejected as allegedly obvious over Becker in view of Kuby, Adair and Janeway. The Examiner alleges that it would have been obvious to select a human lgG1 isotype either for higher binding affinity as allegedly taught by Adair and Kuby or because in the absence of unexpected results selection from a finite number of isotypes does not constitute a patentable invention.

As to the first point, the Gadai declaration pointed out that not only is there no general rule that human IgG1 isotype has a higher binding affinity that other human isotypes, but provided an example in which human IgG1 has the lowest binding strength of the four human isotypes (see paragraph (3)). Thus, a skilled person would not have been motivated to select human IgG1 based on its binding strength.

As to unexpected results, a direct comparison between human isotypes in humans is not currently practical because conducting even a single clinical trial on sufficient patients to provide significant evidence of efficacy is an extremely expensive proposition. Comparing human isotypes in a mouse model is also difficult because human isotypes may be subject to a mouse-anti-human response, which can obscure evidence of comparative efficacy of different isotypes. However, evidence of unexpected results of human IgG1 has been obtained inferentially by comparison of antibodies with different mouse isotypes. As was discussed earlier in prosecution, the closest mouse equivalent of human IgG1 is mouse IgG2a, which has

the property of strongly interacting with complement and Fc gamma receptors. By contrast, human IgG2 and IgG4, which interact less well with complement and Fc gamma receptors are closest to mouse IgG1 and mouse IgG2b to human IgG3 (see, e.g., Gadai declaration and Hussain, *Clinical Diagnostic Lab. Immunol.* 2, 726-732 (1995) (of record).

Bard, PNAS 100, 2023-2028 (2003) (cited as cite no. 550 by the supplemental IDS filed April 25, 2005) provides evidence that mouse antibodies of isotype IgG2a were more effective not only in clearing amyloid deposits but also in similarly reducing neuritic dystrophy in a mouse model than either mouse IgG1 or mouse IgG2b (see Fig. 4). These results suggest that clearing of amyloid deposits by an antibody-mediated phagocytosis model leads to a reduction of neuritic pathology, and is promoted by selection of an antibody of mouse Ig2a isotype, which is most conducive to inducing phagoctytosis. This result is surprising for several reasons. Insofar as the art had considered antibodies in the context of Alzheimer's disease it was by a mechanism of inhibiting amyloid toxicity (Becker) or inhibiting Aβ aggregation (see, e.g., Solomon , PNAS, 93:452-455 (1996) (cited as cited no. 160 by the supplemental IDS filed April 6, 2000). Because Becker does not mention including either complement or phagocytic cells in the in vivo neurotoxicity assays proposed for screening antibodies, it can be inferred that the envisaged mechanism is one of simply binding. The same is true of the proposal by Solomon et al. in which antibodies to Aβ are used to inhibit Aβ aggregation. Either of these mechanisms can be effected by simple binding of an antibody to Aβ, would not require an antibody to interact with phagocytic cells to induce amyloid clearing, and would not be expected to be facilitated by selecting an isotype that would interact well with complement and Fc receptors.

The result was also unexpected because of the view that Alzheimer's was at least in part mediated by inflammation and stirring up the immune response would only make things worse.

> The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to the destruction of brain cells.
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> Okie, S., *Washington Post,* page A01 (May 8, 2001) (cited as cite no.841 by the supplemental IDS filed April 16, 2007).

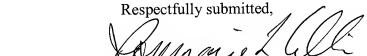
Although interactions between antibodies and Fc receptors can be useful against pathogens they can also contribute to undesired inflammation and autoimmunity (*see* Hogarth, *Current Opinion in Immunology* 2002, 14:798–802, IDS cite no. 1193; and, US 5,624,821 IDS cite no 718). According to such a view, selection of an isotype that interacted most strongly with complement and Fc receptors would be counter-indicated because of concern that inflammation from these interactions would only make things worse.

Given the background that antibodies were proposed to operate by mechanisms not requiring effector functions, and the concern that an isotype offering strong effector function might exacerbate an inflammatory component of Alzheimer's disease, the result that mouse IgG2a and by inference human IgG1, which has the strongest effector functions, is the most effective isotype not only in clearing amyloid deposits but in reducing neuritic dystrophy can only be regarded as unexpected.

¶¶11-20. All of the remaining art rejections are also premised on the allegation that the combination of Kuby, Janeway and Adair would have rendered obvious the selection of a human IgG1 isotype in the claimed methods. The distinctions discussed above are thus equally applicable.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Rosemarie L. Celli
Reg. No. 42,397

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
JOL:RLC
62732955 v1